The cutting edge

A synergy of modern surgical techniques and science improves patient survival and recovery

Archaeological finds have shown that early humans performed crude operations on one another many thousands of years ago. Since then, surgery has remained one of our most important tools to deal with the consequences of disease, accidents and ageing. Yet, surgery has advanced greatly since the days when primitive humans drove stones into one another's skulls to release demons. Both social trends and basic research have improved surgical techniques, survival and recovery times. Advances in imaging technologies and molecular tests allow for the earlier and more accurate diagnosis of disease—which has increased the likelihood of success of the subsequent surgery—and advances in imaging have improved the accuracy of the surgery itself, and have reduced collateral damage and the unnecessary destruction of healthy tissues and cells (Sullivan & Kelloff, 2005).

In fact the first major reduction in collateral damage came a generation ago with the introduction of micro- and keyhole surgery, which use laparoscopic techniques—the insertion of small and remotely operated instruments through small incisions—to perform operations. The latest innovation in this regard is called 'natural orifice transluminal endoscopic surgery' (NOTES), or 'orifice surgery', because it uses the natural openings of the body to access the site of the operation. The surgeon inserts the surgical tools into the orifice and guides them to the surgical site with the assistance of imaging or scanning technology. In addition, the endoscope through which the tools were inserted can then be used to observe and direct the surgery itself.

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Although the first pure NOTES operations using tools and cameras inserted through an orifice and remote incisions inside the patient have yet to be performed, the technique has been used in at least two hybrid operations that have combined laparoscopy and endoscopy. Although there is some confusion between the two terms, endoscopy is generally understood to involve inserting equipment into an orifice and, more recently, has often been used for the removal of small amounts of tissue for biopsy. By contrast, laparoscopy generally involves the surgeon making a number of external incisions through which to insert the laparoscope, and is already used for several surgical procedures such as laparoscopic cholecystectomy or appendectomy. In hybrid operations, surgeons insert an endoscope carrying the surgical tools, but also make small incisions to help with imaging through a laparoscope.

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One of the first hybrid NOTES operations was performed in March 2007 at the Columbia University Medical Centre in New York (NY, USA), in which a woman's gall bladder was removed through an incision in her vaginal wall (USGI, 2007). The surgeons made a series of small abdominal incisions and used traditional laparoscopy to insert imaging instruments to guide the surgical tools. Just two weeks later, a team in Strasbourg, France, performed a similar operation but used only one small laparoscopic incision, which, in time, would leave virtually no noticeable scar (Marescaux *et al*, 2007).

To avoid the need for laparoscopic assistance altogether, a surgical team would need imaging techniques such as external scanning or cameras to accompany the surgical tools through an endoscopic tube. External scanning alone is unlikely to yield the required precision, but it could be combined with a small camera inserted through the endoscope. Such instruments—for example, the minute fibre-optic cameras that are used in optical coherence tomography (Hunter, 2007)—are now being tested in the laboratory. Surgical applications might also soon be a possibility: the Oregon Clinic (Portland, OR, USA), which recently performed the first gall bladder removal through the mouth and the stomach (Oregon Clinic, 2007), has stated that it now has the technology available.

In fact, there are a handful of companies that now make the specialized technology needed to perform NOTES operations. One of the pioneers is USGI Medical in San Clemente, CA, USA, which provides the two crucial components needed for the insertion and control of the surgical tools. The first component, the Shapelock Endoscopic Guide, comprises a flexible loop-like structure that the surgeon can insert through the orifice and which then bends to fit the anatomy of the patient. This creates a stable channel through which the tools can be inserted and guided to the site of the operation. The second component, which USGI calls the Endosurgical Operating System, comprises the technology for imaging and controlling the tools during the operation.

Although endoscopic surgery reduces the amount of external scarring associated with traditional and laparoscopic surgery, it does not remove the need for incisions altogether; it just internalizes them. Indeed, because the cuts are internal, they are harder to monitor and the risk of infection increases when conventional antiseptic procedures cannot be used. The main technical challenge therefore lies in developing reliable ways of closing internal incisions and avoiding infection. Conversely, because the incisions are internal, post-operative pain is minimal as internal organs are relatively free of nerves, unlike the abdominal wall and parietal peritoneum that have to be cut through in conventional or keyhole operations. Proponents of NOTES also claim that recovery times are faster and hospital stays reduced, even compared with modern laparoscopic keyhole surgery, because the incisions are both smaller and in places that tend to heal more quickly.

A persistent challenge for surgery and surgeons is the need to cut through layers of tissue and to traverse considerable distances to reach the site of the operation. In this regard, robots might soon provide skilled assistance by taking over some of the more routine aspects of an operation. In the case of NOTES surgery, robots have a particularly promising application in targeting the surgical instruments to the site of the operation through the endoscopic channel. However, Professor Guang-Zhong Yang, Director of Medical Imaging and Robotics at Imperial College, London, UK, noted that we are a long way from surgeons being replaced by robots altogether; rather, the robots are intended to enhance the surgeon's skill. For example, Yang mentioned a research project under way at Imperial College using a technique called perceptual docking, which provides enhanced sensual feedback to the surgeon in real time. Docking normally refers to the process of moving a robot to the correct position and orientation from which to perform a task. The perceptual docking concept will extend this so that "the machine can adapt to the behaviour of the surgeon and work only within the safety margin prescribed by the surgeon," Yang said. "This leaves the surgeon to concentrate on more complex tasks that cannot easily be performed by the robot."

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Yet, the robots will not just be the surgeons' handmaids. Rather, their role will be that of a sous-chef that can effectively contribute to the operation, particularly in surgery to remove tumours. In this specific case, the use of a robot should minimize the size of the surgical margin—the area that defines the excess tissue to be cut away to remove all possible malignant cells. As Yang noted, the current focus on robotics research is integrating with advanced imaging technologies to assess the tissue and identify cancerous cells, thus keeping the margins tight (Hunter, 2007). "Laparoscopic ultrasound is now increasingly used in interventional procedures, and in the near future there will be more imaging modalities used in surgery, particularly optical imaging techniques such as multi-excitation laser induced fluorescent imaging," Yang said. "In cancer procedures, this permits accurate determination of tumour margins *in situ* using non-contact, imaging based biopsies to avoid further metastases and cancer-cell seeding." Yang also believes that robotics will help to disseminate best practice because they will undertake tasks that can be clearly defined, in the same way that computers onboard an aircraft can help to eliminate human error. "[R]obotic techniques extend the capability of the human by improving the consistency, safety and dexterity of the surgeon," he said.

New imaging techniques also extend the range of operations that can be performed under local anaesthetic. Technologies such as three-dimensional ultrasound imaging can be used to locate individual nerves to anaesthetize, instead of using a general anaesthetic. The technology is a refined version of the ultrasound scanning used to show expectant mothers images of their developing fetuses and, given sufficient sensitivity and focusing ability, an ultrasound scanner can identify nerves because of their fatty sheaths, which readily reflect high-frequency sound waves.

Anaesthetists at the Mayo Clinic in Jacksonville, FL, USA, have demonstrated the use of three-dimensional ultrasound to block nerves in 150 varieties of surgery at several presentations during 2007. One such operation used the sciatic nerve behind the thigh of a woman who needed major reconstructive surgery on her foot; anaesthetists placed a catheter filled with local anaesthetic next to the nerve to block pain signals from just that specific area. Even more remarkably, a Mayo anaesthetist, Roy Greengrass, recently used three-dimensional ultrasound to remove a major tumour in a patient's middle ear under local anaesthetic—an operation that would usually have required a general anaesthetic. As another Mayo Clinic anaesthetist, Steven Clendenen noted, the key to extending local anaesthesia lies in combining three-dimensional imaging with a detailed anatomical knowledge of nerve locations and the areas that they serve. Furthermore, three-dimensional imaging also allows the spread of the anaesthetic to be monitored after administration so that the surgeon can begin to work as soon as pain relief has taken effect, but no sooner.

Yet, even with the application of three-dimensional ultrasound imaging, a general anaesthetic will probably always be required for major abdominal, chest and heart surgery. In fact, it was the invention of general anaesthesia that made invasive surgery possible in the first place and, as Clendenen commented, there is no firm evidence that it is more dangerous than local anaesthesia for reasonably healthy patients. The use of local anaesthesia would mainly benefit the elderly or seriously ill patients for whom the trauma of a general anaesthesia carries a serious risk of complications or death. "There are many patients […] where local is much safer than general anaesthesia," Clendenen said. "The benefits of regional anaesthesia include less narcotics required with less side effects associated with them, overall improved patient satisfaction and less pain. We are now sending patients home with peripheral nerve catheters that would otherwise require a prolonged hospital stay."

Other improvements in surgical techniques are using heat and light applied through an endoscope to carefully target tumours—helping to remove the need for invasive incisions altogether. Photodynamic therapy has already been used successfully for tumours of the oesophagus and digestive tract, which can be easily reached using standard endoscopic equipment. The technique involves the use of a photosensitizing drug, which is absorbed by all the cells of the body but lingers in cancerous cells for longer. Once most of the drug has left the non-cancerous cells, radiation is administered to the target area, typically through fibre-optic tubes. The irradiated cells then die from a combination of local heating, oxidation and the destruction of small blood vessels that supply the tumour. The disadvantage of this procedure is the need for the photosensitizer, but this is outweighed by the many advantages. According to Professor Steve Bown, Director and Founder of the UK National Medical Laser Centre at University College London, UK, the biggest benefit is the repeatability of the treatment because there is no cumulative effect. In addition, photodynamic therapy is well suited to deal with very small and possibly scattered tumours, and to nipping out pre-cancerous cells before they become dangerous or malignant.

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The combination of photodynamic treatment with so-called focal therapy would avoid the need to systemically administer a photosensitizing drug. Focal therapy uses imaging techniques to identify and locate tumours more precisely and to administer the photosensitizer locally. This reduces the damage to the surrounding tissue and improves the patient's prognosis and quality of life. Focal therapy has been most widely applied to treat prostate cancer to reduce the subsequent risks of impotence and incontinence. The University College London, UK, is now conducting a phase II trial of photodynamic and focal therapy in prostate cancer. According to the college's clinical research fellow and honorary consultant urologist Hashim Ahmed, the early results are promising, although long-term studies are required to establish that the technique does improve the overall outcome. Ahmed is convinced that focal therapy represents an improvement, even over ultrasound treatment, which has already reduced the risk of incontinence. "High-intensity focused ultrasound has a long established literature although the results in prostate cancer are medium term only. The incontinence rates are low (~8%) but the impotence rate is still high (~40–50%)," he said. "Hence, the need for focal therapy."

Yet, there are many diseases that are not amenable to surgery, such as distributed cancer, autoimmune and immunodeficiency diseases, and many neural degenerative diseases. For diseases that require intervention at the molecular level, stem-cell or gene therapies are likely to have a great impact, often opening new fields for surgical applications. One such example is a new gene therapy to tackle Parkinson disease that has shown promising results in a phase I trial at Columbia and Cornell University's New York-Presbyterian Hospital, NY, USA (Kaplitt *et al*, 2007).

Matthew During, Professor of Molecular Medicine at the University of Auckland, New Zealand, and his team developed an experimental gene therapy to combat the degeneration of dopamine-producing cells in the brains of Parkinson patients. The gene therapy works by re-establishing the normal activity of neural motor circuits by targeting the gene that produces γ-aminobutyric acid (GABA)—the main inhibitory neurotransmitter in the brain. The researchers packaged the glutamic acid decarboxylase (GAD) gene responsible into an adeno-associated virus for delivery to the target cells, but the procedure requires surgery to get the virus to the affected areas of the brain. According to During, the therapy restores normal brain chemistry with a 25–30% increase in the Parkinson disease-rating score—a major improvement in the quality of life of the patients.

Similar therapies based on therapeutic stem cells or proteins might also rely on surgery to deliver the therapy to its target when oral administration or injection are not possible. Surgery is therefore not an old technique that is soon to be replaced by new miracle drugs born of molecular biology. In fact, research into robotics, imaging and molecular biology is carrying surgery into a new era, expanding its role and refining its conduct, just as improved tools and scanning technology did a generation ago with the advent of keyhole surgery.

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